05/26/04

IFW

AF

1654

Express Mail Label No. EV 394802148 US
Attorney Docket No. UNI.19

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

APPLICANT:	JIA
SERIAL NO.:	10/091,362
FILED:	MARCH 1, 2002
TITLE:	IDENTIFICATION OF FREE-B-RING FLAVONOIDS AS POTENT COX-2 INHIBITORS

EXAMINER: MELLER, M. V.
ART UNIT: 1654
CONF. NO. 7281

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

REPLY TO EXAMINER'S ANSWER TO BRIEF FOR APPELLANT

A Notice of Appeal to the Board of Appeals was filed in the above-referenced application on October 29, 2003 and an Appeal Brief was filed on December 29, 2003. The Examiner issued a Response to the Appeal Brief on March 24, 2004. In said Response, the Examiner concluded that the rejections should be sustained. This Reply is filed in response to the Examiner's response.

Rejections under 35 U.S.C. § 102

The Examiner has rejected claims 1, 4, 7, 24-26 and 32-34 under 35 U.S.C. § 102(a) as being anticipated by Chi *et al.* (2001) Biochemical Pharmacology 61:1417-1427 or Chen *et al.* (2001) Biochemical Pharmacology 61:1195-1203. The Examiner provides that each of these references "teach that an extract from *Scutellaria baicalensis* is administered to a patient to inhibit or suppress COX-2."

The Chi *et al.* Reference

Chi *et al.* ((2001) Biochemical Pharmacology 61:1195-1203) demonstrate that wogonin, a free-B-ring flavonoid, inhibits nitric oxide (NO) as well as PGE2 production via suppression of the induction/gene expression of both iNOS and COX-2 in LPS-induced RAWcells (page, 1200, col. 1). The wogonin used in this study was isolated from *Scutellaria radix* and was >95% pure. (page 1196, col 1). Thus, contrary to the Examiner's assertion Chi *et al.* do not teach administering an extract isolated from *Scutellaria baicalensis* to inhibit or suppress COX-2. Rather, Chi *et al.* teach administering a single compound isolated from *Scutellaria radix* to inhibit NO as well as PGE2 production. The authors provided that although the reason for the various sensitivities to inhibition by wogonin was not known, "[i]t may be explained in part by the fact that, in addition to the suppressive effects of wogonin on iNOS and COX-2 induction, it also inhibited COX-2 activity." (page 1200; col. 1). In the Response to Argument Section of the Examiner's response, the Examiner maintains that "Chi teaches that wogonin suppresses the activity of COX-2, see title." It is clear that Chi *et al.* are merely speculating that wogonin directly inhibits the COX-2 enzyme as it was expressly stated that the reason for the various sensitivities was not known.

As noted in Appellant's Brief, claim 1 of the instant invention is drawn to a method for inhibiting the COX-2 enzyme by administering a composition comprised of 10% to 100% of a mixture of free-B-ring flavonoids. The Chi *et al.* reference does not disclose or suggest a composition of matter comprised of a mixture of free-B-ring flavonoids, but rather discloses the purported effect of one free-B-ring flavonoid, wogonin on COX-2 inhibition. With reference to the Specification, it can be seen that relative to the other free-B-ring flavonoids tested, such as baicalein (100% inhibition) and baicalin (97% inhibition), wogonin is actually a relatively poor COX-2 inhibitor (12% inhibition). (Specification, page 25, Table 4). Since claim 1 is drawn to a composition comprised of a mixture of free-B-ring flavonoids neither this claim nor the claims that depend from this claim are anticipated by the Chi *et al.* reference.

Independent claim 24 is drawn to a method for inhibiting the COX-2 enzyme by administering a composition comprised of 10% to 100% of a single free-B-ring flavonoid, wherein said free-B-ring flavonoid is selected from the group consisting of baicalein, 5,6-dihydroxy-7-methoxyflavone, 7,8-dihydroxyflavone and baicalin. Claim 24 does not include the free-B-ring flavonoid wogonin and is therefore not anticipated by the Chi *et al.* reference. For

the same reason the claims that depend from independent claim 24 are also not anticipated by the Chi *et al.* reference.

The Chen *et al.* Reference

Chen *et al.* ((2001) Biochemical Pharmacology 61:1417-1427) examined three free-B-ring flavonoids: wogonin, baicalin and baicalein for their effects on LPS-induced NO production and iNOS and COX-2 gene expression. As noted in Appellant's Brief, gene expression is a measure of mRNA production from DNA and further, gene expression down regulation does not necessarily lead to inhibition of the protein itself. In this study, Chen *et al.* also indirectly examined the effects of baicalin, baicalein and wogonin on iNOS and COX-2 enzyme activity, as described in Section 3.3 beginning on page 1420 of the reference. The authors conclude that "[w]ogonin, but not baicalin or baicalein, inhibited LPS-induced COX-2 expression." (page 1426, col. 1). The authors also expressly provide that "[t]hese compounds [wogonin, baicalin and baicalein] did not affect iNOS and COX-2 (enzyme) activity." (Page 1426, col. 1). Thus, contrary to the Examiner's assertion, Chen *et al.* found no direct enzyme inhibition by any of the three free-B-ring flavonoids evaluated. The baicalin, baicalein and wogonin used in this study were isolated from *Scutellaria baicalensis* and the purity of each of the compounds was determined to be >99.5%. (page 1418, col. 2). Thus, Chen *et al.* do not teach administering a mixture of free-B-ring flavonoids isolated from *Scutellaria baicalensis* to inhibit or suppress COX-2. Rather, Chen *et al.* teach administering three individual compounds isolated and purified from *Scutellaria baicalensis* to determine their effects on LPS-induced NO production and iNOS and COX-2 gene expression.

The Examiner has rejected claims 1, 4, 7, 24-26 and 32-34 under 35 U.S.C. § 102(e) as being anticipated by Xinxian, U.S. Pat. No. 6,290,995; Newmark *et al.*, U.S. Pat. No. 6,264,995; Newmark *et al.*, U.S. Pat. No. 6,391,346; Newmark *et al.*, U.S. Pat. No. 6,387,416 or Kuhrts, U.S. Pat. No. 6,475,530. The Examiner provides that each of these references "teach that an extract from *Scutellaria baicalensis* is administered to a patient to inhibit COX-2 or to treat cancer which is also regulated by COX-2."

The Xinxian Reference

Xinxian (U.S. Pat. No. 6,290,995) teaches a method for producing a pharmaceutical composition of baicalin in combination with the alkaloid berberine for use in the treatment of cancer and control of cancer cells. The Xinxian patent does not teach or suggest that the free-B-ring flavonoid, baicalin, isolated from *Scutellaria baicalensis* inhibits COX-2 activity. Nor does the Xinxian patent disclose or suggest an active composition of matter comprised of a mixture of free-B-ring flavonoids. Finally, although there may be some overlap between indications requiring an inhibitor of DNA synthesis etc. and those requiring a COX-2 inhibitor, there is no evidence to suggest that the overlap would be substantial. That is to say that there are likely to be diseases or conditions, in which a COX-2 inhibitor would be indicated for which an inhibitor of DNA synthesis would not be effective and visa versa. In the Response to Argument Section of the Examiner's response, the Examiner maintains that "if cancer is inhibited so is the COX-2 activity inherently." The Examiner however, provides no support for the assertion that any composition that inhibits cancer also inherently inhibits COX-2 activity. As stated above, the law is clear that to anticipate a claim, a prior art reference must disclose every limitation of the claimed invention either expressly or inherently. Applicant maintains that the Xinxian reference does not anticipate the claims of the instant invention.

The Newmark References

Newmark *et al.* (U.S. Pat. No. 6,264,995, the '995 patent), teach an herbal composition, which contains extracts from 13 different plants, including *Scutellaria baicalensis*. The patent provides that the extract reduces inflammation in bones and joints by inhibiting the COX-2 enzyme. The only definition of the *Scutellaria baicalensis* root extract is 5:1, which generally refers to 5 parts of plant root yielding one part of the extract. Considering that more than 58 compounds have been isolated from *Scutellaria baicalensis*, a hydroalcoholic extract could contain any number of compounds including, but not limited to alkaloids, benzyl alcohol glycosides, lignans, benzopyranones, amino acids, phytosterols, monosugars, flavones and flavanones. The '995 patent does not teach or suggest the use of free-B-ring flavonoids or mixtures thereof as COX-2 inhibitors. The present invention, on the other hand, discloses and claims a specific class of compounds, free-B-ring flavonoids, as having COX-2 inhibitory activity. Thus, even though the Newmark *et al.* composition likely contains free-B-ring flavonoids, there is no disclosure or suggestion that these compounds are COX-2 inhibitors.

Additionally, with reference to the Table provided in the Newmark patent (col. 12), the extract of *Scutellaria baicalensis* accounted for approximately 2.6% by weight of the formulation. As discussed in detail in Applicant's Appeal Brief, the amount of free-B-ring flavonoid or mixtures thereof in the formulation taught by Newmark *et al.* is significantly less than the amount set forth in the claims of the instant invention.

Newmark *et al.* (U.S. Pat. No. 6,387,416), describe an orally or topically administered composition capable of reducing inflammation. With reference to the Table (col. 8-9), the maximum % of baicalin in the formulation described in this patent is approximately the same as the '995 patent. Additionally, as discussed above Newmark *et al.* neither teach nor suggest the use of free-B-ring flavonoids as COX-2 inhibitors. Therefore, based on the reasoning above, this patent does not anticipate the claims of this invention.

Newmark *et al.* (U.S. Pat. No. 6,391,346), describe an orally administered composition capable of reducing inflammation in animals. As discussed in detail in Applicant's Appeal Brief, the amount of free-B-ring flavonoid or mixtures thereof in the formulation taught by Newmark *et al.* is less than the amount set forth in the claims of the instant invention. Additionally, as discussed above Newmark *et al.* neither teach nor suggest the use of free-B-ring flavonoids as COX-2 inhibitors. Therefore, based on the reasoning above, this patent does not anticipate the claims of this invention.

The Kuhrts Reference

Kuhrts (U.S. Pat. No. 6,475,530) describe weight loss compositions that combine a weight loss effective compound and a botanical COX-2 inhibitor. As noted by the Examiner, the plant "*Scutellaria baicalensis*" was referred to in the patent as a COX-2 inhibitor. There is no further description, however, of the material or extract of *Scutellaria baicalensis* being used. Nor is there any reference to amounts or dosage. Nor does the Kuhrts patent teach or suggest the use of free-B-ring flavonoids or mixtures thereof as COX-2 inhibitors. Therefore, Applicant maintains that the Kuhrts patent does not anticipate the claims of the instant invention.

Rejections under 35 U.S.C. § 103

The Examiner has rejected claims 1, 4, 7, 22, 24-27 and 32-34 under 35 U.S.C. § 103(a) as being unpatentable over Chi *et al.* (2001) Biochemical Pharmacology 61:1417-1427; Chen *et al.* (2001) Biochemical Pharmacology 61: 1417-1427; Xinxian, U.S. Pat. No. 6,290,995;

Newmark *et al.*, U.S. Pat. No. 6,264,995; Newmark *et al.*, U.S. Pat. No. 6,391,346; Newmark *et al.*, U.S. Pat. No. 6,387,416; or Kuhrts, U.S. Pat. No. 6,475,530 for the reasons set forth above with respect to the Section 102 rejections. The Examiner asserts that "[t]he amounts used are simply the choice of the artisan to use in an effort to optimize the desired results." The Examiner also provides that "the range of 2.0 to 200 mg/kg of body weight is a very broad range [and] . . . that it is within the purview of the skilled artisan to use such broad ranges." Contrary to the Examiner' assertion however, Applicant maintains that in the case of chemical compounds slight changes, including a mere change in the amount of a compound, have been found to be sufficient to change an old compound into a new one. (Schering Corp. v. Precision-Cosmet Co. 614 F. Supp. 1368, 1374 (D. Del. 1985)). As noted above, the present invention is drawn to a method for inhibiting the COX-2 enzyme by administering a composition comprising 10% to 100% of a specific free-B-ring flavonoid (claim 24) or mixtures thereof (claim 1).

Chi *et al.* ((2001) Biochemical Pharmacology 61:1195-1203) demonstrate that wogonin, a free-B-ring flavonoid, inhibits nitric oxide (NO) as well as PGE2 production via suppression of the induction/gene expression of both iNOS and COX-2 in LPS-induced RAWcells (page, 1200, col. 1). The Chi *et al.* reference does not disclose or suggest a composition of matter comprised of a mixture of free-B-ring flavonoids, but rather discloses the purported effect of one free-B-ring flavonoid, wogonin on COX-2 inhibition. With reference to the Specification, it can be seen that relative to the other free-B-ring flavonoids tested, such as baicalein (100% inhibition) and baicalin (97% inhibition), wogonin is actually a relatively poor COX-2 inhibitor (12% inhibition). (Specification, page 25, Table 4).

Chen *et al.* ((2001) Biochemical Pharmacology 61:1417-1427) examined three free-B-ring flavonoids: wogonin, baicalin and baicalein for their effects on LPS-induced NO production and iNOS and COX-2 gene expression. In this study, Chen *et al.* also indirectly examined the effects of baicalin, baicalein and wogonin on iNOS and COX-2 enzyme activity, using a cell model of LPS stimulated prostaglandin E2 (PGE2) production. As noted above, the authors conclude that "[t]hese compounds [wogonin, baicalin and baicalein] did not affect COX-2 (enzyme) activity." (Page 1426, col. 1). Thus, Chen *et al.* found no direct enzyme inhibition by any of the three free-B-ring flavonoids evaluated. Applicant maintains that when combined with the Chi reference, there would be little motivation to use a free-B-ring flavonoid or mixtures thereof as potential COX-2 inhibitors. While the Chi *et al.* reference merely speculates that

wogonin inhibits the COX-2 enzyme, the Chen *et al.* reference expressly provides that there was no direct COX-2 inhibition by any of the free-B-ring flavonoids tested.

Xinxian (U.S. Pat. No. 6,290,995) teaches a method for producing a pharmaceutical composition of baicalin for use in the treatment of cancer and control of cancer cells. The Xinxian patent does not teach or suggest that the free-B-ring flavonoid baicalin inhibits COX-2 activity. Nor does the Xinxian patent disclose or suggest an active composition of matter comprised of a mixture of free-B-ring flavonoids. For these reasons, Applicant maintains that the Xinxian reference does not render the present invention obvious.

Newmark *et al.* (U.S. Pat. No. 6,264,995, the '995 patent), teach an herbal composition, which contains extracts from 13 different plants, including *Scutellaria baicalensis*. The patent provides that the extract reduces inflammation in bones and joints by inhibiting the COX-2 enzyme. As noted above, the '995 patent does not teach or suggest the use of free-B-ring flavonoids or mixtures thereof as COX-2 inhibitors. The present invention, on the other hand, discloses and claims a specific class of compounds, free-B-ring flavonoids, as having COX-2 inhibitory activity. Thus, even though the Newmark *et al.* composition likely contains free-B-ring flavonoids, there is no disclosure or suggestion that these compounds are COX-2 inhibitors. Applicant maintains that there are many advantages to isolating and identifying specific biologically active compounds from a composition of matter that could contain literally thousands of compounds. Once identified a class of compounds can be purified and concentrated to provide a more effective biological agent. Additionally, the compounds can be chemically modified to provide a composition of matter that is more active and/or less toxic. Finally, once isolated and identified a specific compound or class of compounds can be studied to determine the exact biological activity and mode of action, thus enabling more specific targeting of the compound or class of compounds to treatment of particular diseases or conditions. Contrary to the Examiner's assertion that optimization of factors such as concentration is standard practice, unless one knows what specific compound or class of compounds is exhibiting the desired activity, one cannot possibly optimize the concentration of that compound or class of compounds. Based upon this reasoning, Applicant asserts that none of the cited Newmark *et al.* patents renders the method of the present invention obvious.

Kuhrts (U.S. Pat. No. 6,475,530) describe weight loss compositions that combine a weight loss effective compound and a botanical COX-2 inhibitor. The plant *Scutellaria baicalensis* was referred to in the patent as a COX-2 inhibitor. There is no further description,

however, of the material or extract of *Scutellaria baicalensis* being used. Nor is there any reference to amounts or dosage. The Kuhrts patent does not teach or suggest the use of free-B-ring flavonoids or mixtures thereof as COX-2 inhibitors. Therefore, for the reasons discussed above, Applicant maintains that the Kuhrts patent does not render the present method obvious.

For the foregoing reasons, Appellant maintains that none of the references cited by the Examiner, either alone or in combination render the present invention obvious and therefore the claims are patentable.

In view of the foregoing arguments, Appellant submits that none of the references cited by the Examiner, either alone or in combination anticipate the claims of the instant invention or render the present invention obvious. It is therefore, respectfully requested that the claims be allowed to issue.

In the Response to Argument Section of the Examiner's response, the Examiner maintains that "some of the . . . extracts are taught to inhibit COX-2 while others are not, but that all that is needed to meet the claims is that one of the claimed [compounds] inhibit COX-2." In response argument Applicant maintains that claim 1, is drawn to a mixture of free-B-ring flavonoids each of which, as noted above, exhibit different activity with respect to COX-2. Applicant maintains that even if for the sake of argument one of the minor components in that mixture (i.e. wogonin) was slightly biologically active, it would not render the mixture or other individual compounds in the family anticipated or obvious.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to Deposit Account No. 19-5117 if not otherwise specifically requested. In addition, the undersigned authorizes the charge of any additional fees associated with the filing of this document to Deposit Account No. 19-5117.

Respectfully submitted,

Date May 24, 2004

Rosemary Kellogg, #39,726
Swanson & Bratschun, L.L.C.
1745 Shea Center Drive, Suite 330
Highlands Ranch, Colorado 80129
Telephone: (303) 268-0066
Facsimile: (303) 268-0065